REMARKS

I. Status Summary

Claims 23-30 and 32-46 are pending in the present application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office"). Claims 23-30 and 32-46 currently stand rejected.

Claims 23, 26-28, 30, 32-35, 37-40 and 43-46 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over PCT International Patent Application Publication No. WO 98/33527 to Cohen (hereinafter "Cohen").

Claims 23, 25-28, 30, 32-40 and 43-46 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Cohen in view of PCT International Patent Application Publication No. WO 01/36680 to Eastman et al. (hereinafter "Eastman et al.") and PCT International Patent Application Publication No. WO 02/36790 to Schuller et al. (hereinafter "Schuller et al.").

Claims 23, 24, 26-30, 32-35 and 37-46 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Cohen in view of PCT International Patent Application Publication No. WO 98/33527 to Warnier et al. (hereinafter "Warnier et al.").

Claims 23, 27 and 33 have been amended herein. Support for the amendments can be found throughout the specification as originally filed, and particularly in the last full paragraph of page 7. No new matter has been added.

New claims 47-49 have been added. Support for the new claims can be found throughout the specification as originally filed, and in particular at page 6, last paragraph bridging page 7, through the second full paragraph of page 7. No new matter has been added.

Reconsideration of the application in view of the amendments and remarks set forth herein is respectfully requested.

II. Responses to the Obviousness Rejections

Claims 23, 26-28, 30, 32-35, 37-40 and 43-46 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Cohen. Claims 23, 25-28, 30, 32-40 and 43-46 have been rejected under this section upon the contention that the claims are unpatentable over Cohen in view of Eastman et al. and Schuller et al. Claims 23, 24, 26-30, 32-35 and 37-46 have been rejected under this section upon the contention that the claims are unpatentable over Cohen in view of Warnier et al.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

II.A. Response to the Rejection over Cohen

Claims 23, 26-28, 30, 32-35, 37-40 and 43-46 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Cohen.

Initially, applicants respectfully submit that the presently disclosed and claimed subject matter was previously found by the United States Patent and Trademark Office (hereinafter "the Patent Office") to be patentable over Cohen. In particular, applicants respectfully submit that the instant claims were rejected under 35 U.S.C. § 102(b) over Cohen; 35 U.S.C. § 103(a) over Cohen in view of Kugler et al. (2000 *Nature Medicine* 6:332-336; hereinafter "Kugler et al."); 35 U.S.C. § 103(a) over Cohen in view of Kugler et al.; PCT International Patent Application Publication No. WO 01/36680 to Eastman et al. (hereinafter "Eastman et al."); and PCT International Patent Application Publication No. WO 02/36790 to Schuller et al. (hereinafter "Schuller et al.") in the Official Action of June 28, 2006. In the subsequent response on September 29, 2006, applicants traversed these rejections. Then, in view of the response of September 29, 2006, the Patent Office withdrew each of the above-noted rejections based on Cohen in the Official Action of December 27, 2006. Thus, the Patent Office clearly considered the instant claims to be patentable over Cohen. The present claims are believed to be patentable over Cohen for at least the same reasons. As such, applicants respectfully submit that the instant rejection under 35 U.S.C. § 103(a) based on Cohen fails for at least the same reasons as the previous rejections in the Official Action of June 28,

2006. Accordingly, the instant rejection is believed to be improper and should therefore be withdrawn at this time.

Further, the Patent Office concedes that Cohen uses semi-allogeneic APCs but does not teach the use of haploidentical antigen-presenting cells for transfection with tumor-derived DNA. However, the Patent Office asserts that it would have been *prima facie* obvious for one of ordinary skill in the art to use maternal or paternal APCs as a source of HLA-haploidentical APCs in the methods of treating tumors. The Patent Office contends that one of ordinary skill in the art would have been motivated to do so in order to quickly provide a donor APC which was semi-allogeneic rather than having to recombinantly construct such a donor cell or search for a semi-allogeneic cell from an unrelated donor.

Applicants respectfully disagree. Applicants respectfully submit that the instant rejection appears to be premised, at least in part, on the Patent Office's incorrect understanding of "haploidentical". The use of "haplo" derives from *haploid* which represents the genetic constellation in the egg or the sperm which is combined in the *diploid* zygote to form a new individual. HLA-haploidentical is correctly referred to as sharing of an HLA haplotype (i.e. the HLA region on chromosome 6, which includes three MHC class I alleles and 3 MHC class II alleles). In haploidentical individuals, cells, APCs, etc. the shared HLA haplotype is identical by genetic descent, i.e. the individuals, cells, APCs, etc. are genetically related. That is, the shared HLA-haplotypes are haploidentical because they are genetically identical by descent from the same parent. Importantly, because the chromosomes are passed on to the next generation through the sperm and the egg, the entire genetic information of all 3 HLA class I alleles and all 3 HLA class II alleles will be genotypically identical on shared HLA haplotypes, i.e. HLA-haploidentical.

There is great diversity in the HLA genetic system, which is the most polymorphic genetic system in man. Therefore when cells or APCs are derived from two unrelated individuals they are referred to as allogeneic. If cells or APCs are derived from the same individual they are referred to as syngeneic. By genetic typing it is possible to identify unrelated individuals who are partially or fully matched for HLA alleles. These two individuals are referred to as HLA-matched in the case of genetically identical

sequences or HLA-mismatched, in the case of genetically different sequences for any of the HLA class I or class II alleles. Even if there is a full HLA match for all HLA class I and class II alleles, these individuals are referred to as fully HLA-matched but not as HLA-haploidentical because they are not genetically identical by descent. If there are only partial matches, the cells may be referred to as "semi-allogeneic". The term "semi-allogeneic" may be used for cells of unrelated individuals that share some MHC class I or class II alleles and differ by some class I or class II alleles. Since this is also the case in cells or APCs that are HLA-haploidentical they too may be referred to as semi-allogeneic. However, this is a one-way useage. HLA-haploidentical can be designated as semi-allogeneic but semi-allogeneic does not imply HLA-haploidentical, because semi-allogeneic does not strictly mean identity of one HLA-haplotype by genetic descent.

As noted in the Amendment filed September 29, 2006, Cohen does not teach or suggest the production or use of antigen-presenting cells from donors which are HLA-haploidentical as the term "HLA-haploidentical" is used by applicants in the specification of the present application. The last full paragraph of page 7 of the specification of the present application states as follows:

> HLA-haploidentical antigen-presenting cells have class I (HLA-A, -B, and -C) molecules in common with the patient which are encoded by the HLA-A, -B, and-C alleles of one chromosome. They also have class II molecules (HLA-DR, -DQ, and DP) in common with the patient encoded by the corresponding alleles of the same chromosome.

(emphasis added).

Accordingly, the HLA-haploidentical antigen-presenting cells of the present application and claims 23-30 and 32-46 have each of the class I molecules HLA-A, -B, and -C and each of the class II molecules HLA-DR, -DQ, and -DP that are encoded by the corresponding alleles of a chromosome in common with those of the patient.

In an effort to further clarify the claimed subject matter, applicants respectfully submit that independent claims 23, 27 and 33 have been amended to recite, *inter alia*, "wherein HLA-haploidentical antigen-presenting cells have class I and class II molecules in common with the patient". Support for the amendments can be found

throughout the specification as originally filed, and particularly in the last full paragraph of page 7, as set forth above. No new matter has been added.

In marked contrast, Cohen describes the use of semi-allogeneic cells, rather than specifically HLA-haploidentical cells, and indicates that in one embodiment, "most alleles coding for the various HLA specificities are unmatched between the antigen-presenting cell and the recipient" (*see*, page 23, lines 4-7, of Cohen). Even when Cohen states that the phrase "most alleles being unmatched at the various HLA specificities" refers to unmatched alleles of "from about 50% to less than 100%" (*see*, page 23, lines 7-11, of Cohen), Cohen fails to teach or disclose that all of the alleles encoding both the class I molecules HLA-A, -B, and -C and the class II molecules HLA-DR, -DQ, and -DP on the same chromosome are matched. Even if Cohen's "from about 50% to less than 100%" includes an exactly 50% mismatch of alleles, nothing in Cohen teaches or suggests that the 50% matched alleles must include all of the alleles encoding both the class I molecules HLA-A, -B, and -C and the class II molecules HLA-DR, -DQ, and -DP on the same chromosome. And, numerous possible combinations of 50% matched and 50% unmatched alleles would exist since an APC contains two alleles encoding each MHC molecule, one on each haplotype. For instance, a 50% match could indicate that the alleles on both haplotypes that encode 50% of the MHC molecules are identical to the intended recipient, but that the alleles on both haplotypes that encode the other 50% of the MHC molecules differ from the intended recipient. Thus, the cells having the characteristics described in Cohen would clearly not be HLA-haploidentical to the intended recipient.

To elaborate, Cohen refers repeatedly to the use of cells that are semi-allogeneic and share at least one class I or at least one class II determinant. Nowhere in Cohen is reference made to sharing of class I and class II determinants. Therefore, based on the disclosure of Cohen applicants respectfully submit that one of ordinary skill in the art would not consider the use of HLA-haploidentical cells since one of ordinary skill in the art would understand that HLA-haploidentical cells share both MHC class I and class II alleles. Indeed, since Cohen consistently refers to cells that are semi-allogeneic and share a class I or class II determinant, they are believed to exclude the use of HLA-haploidentical cells.

The exclusion of HLA-haploidentical cells in Cohen is believed to be further reflected in the statement in Cohen that the MHC sharing in the semi-allogeneic cells is about 50% up to 100%. By definition HLA-haploidentical cells share exactly 50% identity, not about 50% up to 100%. Two cells or APCs that are HLA-haploidentical are exactly 50% identical due to sharing of one HLA-haplotype and exactly 50% different due to differences in the second HLA-haplotype which is allogeneic since the chromosomes derive from individuals that are genetically different. Thus, as would be appreciated by one of ordinary skill in the art, applicants respectfully submit that the description of the semi-allogeneic cells in Cohen as having MHC sharing of about 50% up to 100% is believed to clearly exclude HLA-haploidentical cells as presently claimed.

Taken together, applicants respectfully submit that one of ordinary skill in the art would not be motivated to modify the teachings of Cohen as proposed by the Patent Office to arrive at the presently claimed subject matter. Rather, applicants respectfully submit that based on the teachings of Cohen one of ordinary skill in the art would be dissuaded from using HLA-haploidentical cells.

As such, applicants respectfully submit that it is only by using impermissible hindsight reasoning using applicants' own disclosure that the Patent Office can conclude that it would be obvious for one of ordinary skill in the art to employ HLA-haploidentical APCs. As set forth in M.P.E.P. § 2142, "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art" (emphasis added). Given that Cohen fails to teach or suggest the use of HLA-haploidentical APCs, as admitted by the Patent Office, the only disclosure relating to this particular source of APCs is applicants' specification. Since applicants' specification cannot provide the motivation for combining references, applicants respectfully submit that the instant rejection is believed to be improperly based on hindsight.

More particularly, the Patent Office contends that because Cohen allegedly teaches that the paternal or maternal APC would be haploidentical with the patient it would have allegedly been obvious to one of ordinary skill in the art to select maternal or paternal antigen presenting cells. Applicants respectfully disagree. Applicants respectfully submit that Cohen at best notes that "since an individual inherits one

maternal and one paternal chromosome 6, one HLA haplotype is derived from each parent". *See*, page 20, second full paragraph. However, Cohen does not teach or suggest that paternal or maternal APC would be haploidentical as suggested by the Patent Office. Nor does Cohen teach or suggest that it would be obvious to use paternal or maternal APCs. Rather, this assertion by the Patent Office appears to be an interpretation of Cohen with the benefit of hindsight in view of this instant disclosure.

Additionally, applicants respectfully refer the Patent Office to pages 21-24 and the working examples of Cohen. Here, Cohen describes at least three means of obtaining and/or generating semi-allogeneic APCs. In particular, Cohen describes procedures for generating genetically modified APCs that are semi-allogeneic by introducing a nucleic acid molecule coding for a syngeneic determinant. *See*, e.g. page 21 of Cohen. Cohen also describes HLA typing procedures that provide for the screening of APC libraries to identify potential donor semi-allogeneic APCs. *See*, e.g. pages 21-23 of Cohen. Finally, Cohen describes the generation of semi-allogeneic hybrid APCs by fusing an APC with a tumor cell. *See*, e.g. page 23 of Cohen. However, noticeably absent from the disclosure of Cohen is any teaching or suggestion of using HLA-haploidentical APCs, particularly maternal or paternal APCs. Thus, if selecting maternal or paternal APCs would have been obvious as suggested by the Patent Office it would not have been necessary for Cohen to go to such lengths to obtain and/or generate semi-allogeneic APCs, as discussed at pages 21-23 of Cohen. Given that Cohen fails to even mention the use of paternal or maternal APCs as a source of semi-allogeneic APCs, and instead describes other procedures for providing semi-allogeneic APCs, suggests that the presently disclosed and claimed subject matter was not obvious to one of ordinary skill in the art at the time the instant application was filed.

Summarily, in the instant rejection, the Patent Office has provided no basis independent of applicants' disclosure for concluding that one of ordinary skill in the art would have been motivated to employ HLA-haploidentical APCs. Therefore, applicants respectfully submit that the instant rejection is not a case where the Patent Office has only taken into account knowledge asserted to be within the level of one of ordinary skill in the art at the time the claimed invention was made. Rather, the use of applicants'

specification to provide the motivation to modify the reference is improper, and thus the Patent Office has failed to establish a *prima facie* case of obviousness of claims 23, 26-28, 30, 32-35, 37-40 and 43-46 over Cohen.

Accordingly, applicants respectfully submit that the instant obviousness rejection of claims 23, 26-28, 30, 32-35, 37-40 and 43-46 under 35 U.S.C. § 103(a) over Cohen is believed to be improper, and respectfully request that it be withdrawn at this time.

II.B. Response to the Rejection over Cohen in view of Eastman et al. and Schuller et al.

Claims 23, 25-28, 30, 32-40 and 43-46 have been rejected under this section upon the contention that the claims are unpatentable over Cohen in view of Eastman et al. and Schuller et al. The Patent Office contends that Cohen teaches each and every element of the claims except the Patent Office admits that Cohen fails to teach the reverse transcription of amplified cDNA into RNA. However, the Patent Office contends that Eastman et al. and Schuller et al. compensate for this deficiency in the teaching of Cohen. Applicants respectfully disagree.

Initially, applicants respectfully submit that since the instant claims were found to be patentable over the combination of Cohen, Kugler et al., Eastman et al. and Schuller et al., as indicated by the withdrawal of a rejection under 35 U.S.C. § 103(a) in the Official Action of December 27, 2006, it is believed to be axiomatic that the instant claims are now patentable over Cohen, Eastman et al. and Schuller et al. Accordingly, applicants respectfully submit that the instant obviousness rejection is believed to be improper, and respectfully request that it be withdrawn at this time.

Furthermore, without acquiescing to the contentions of the Patent Office applicants respectfully submit that independent claims 23, 27 and 33 have been amended in an effort to further clarify the claimed subject matter. In particular, independent claims 23, 27 and 33 have been amended to recite, *inter alia*, "wherein HLA-haploidentical antigen-presenting cells have class I and class II molecules in common with the patient". Support for the amendments can be found throughout the specification as originally filed, and particularly in the last full paragraph of page 7, as set forth above. No new matter has been added.

Finally, applicants refer to the discussion hereinabove regarding the deficiencies in the teachings of Cohen regarding the use of HLA-haploidentical APCs. Applicants respectfully submit that Eastman et al. and Schuller et al. fail to cure this deficiency. In particular, applicants respectfully submit that there is believed to be no disclosure in either Eastman et al. or Schuller et al. that teaches or suggests the use of HLA-haploidentical APCs as presently claimed. As such, applicants respectfully submit that even assuming *arguendo* that one of ordinary skill in the art would be motivated to combine the references as proposed by the Patent Office, the proposed combination fails to teach or suggest each and every element of the instant claims. Thus, the combination does not render obvious the instant subject matter and therefore fails to support a rejection of the instant claims under 35 U.S.C. § 103(a).

Accordingly, applicants respectfully submit that the instant obviousness rejection of claims 23, 25-28, 30, 32-40 and 43-46 over Cohen in view of Eastman et al. and Schuller et al. is believed to be improper, and respectfully request that it be withdrawn at this time. Applicants further respectfully submit that claims 23, 25-28, 30, 32-40 and 43-46 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

II.C. Response to the Rejection over Cohen in view of Warnier

Claims 23, 24, 26-30, 32-35 and 37-46 have been rejected under this section upon the contention that the claims are unpatentable over Cohen in view of Warnier et al. The Patent Office contends that Cohen teaches each and every element of the claims except the Patent Office admits that Cohen fails to teach using at least one tumor antigen which is suggestive of using multiple tumor antigens. However, the Patent Office contends that Warnier et al. compensates for this deficiency in the teaching of Cohen. Applicants respectfully disagree.

Initially, applicants respectfully submit that since the instant claims were found to be patentable over the combination of Cohen, Kugler et al., Eastman et al., Schuller et al. and Warnier et al., as indicated by the withdrawal of the rejection under 35 U.S.C. § 103(a) in the Official Action of December 27, 2006 on the subject U.S. patent application, it is believed to be axiomatic that the instant claims are now patentable over Cohen and Warnier et al. Accordingly, applicants respectfully submit that the instant

obviousness rejection is believed to be improper, and respectfully request that it be withdrawn at this time.

Furthermore, without acquiescing to the contentions of the Patent Office applicants respectfully submit that independent claims 23, 27 and 33 have been amended in an effort to further clarify the claimed subject matter. In particular, independent claims 23, 27 and 33 have been amended to recite, *inter alia*, "wherein HLA-haploidentical antigen-presenting cells have class I and class II molecules in common with the patient". Support for the amendments can be found throughout the specification as originally filed, and particularly in the last full paragraph of page 7, as set forth above. No new matter has been added.

Finally, applicants refer to the discussion hereinabove regarding the deficiencies in the teachings of Cohen regarding the use of HLA-haploidentical APCs. Applicants respectfully submit that Warnier et al. fails to cure this deficiency. In particular, applicants respectfully submit that there is believed to be no disclosure in Warnier et al. that teaches or suggests the use of HLA-haploidentical APCs as presently claimed. As such, applicants respectfully submit that even assuming *arguendo* that one of ordinary skill in the art would be motivated to combine the references as proposed by the Patent Office, the proposed combination fails to teach or suggest each and every element of the instant claims. Thus, the combination does not render obvious the instant subject matter and therefore fails to support a rejection of the instant claims under 35 U.S.C. § 103(a).

Accordingly, applicants respectfully submit that the instant obviousness rejection of claims 23, 24, 26-30, 32-35 and 37-46 over Cohen in view of Warnier et al. is believed to be improper, and respectfully request that it be withdrawn at this time. Applicants further respectfully submit that claims 23, 24, 26-30, 32-35 and 37-46 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

DISCUSSION OF NEW CLAIMS

New claims 47-49 have been added. Support for the new claims can be found throughout the specification as originally filed, and in particular at page 6, last paragraph bridging page 7, through the second full paragraph of page 7. No new matter has been added.

Applicants respectfully submit that new claims 47-49 are patentable over the references cited by the Patent Office at least for the reasons set forth herein above. Applicants further respectfully submit that new claims 47-49 are allowable over the cited art of record. None of the cited art, either alone or in combination, teaches or suggests each and every element of new claims 47-49. Accordingly, allowance of these claims is respectfully requested.

CONCLUSION

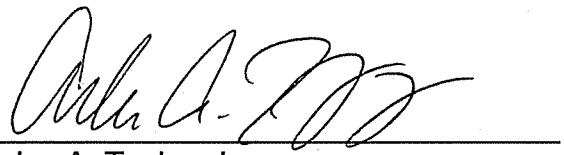
In light of the above, it is respectfully submitted that the present application is now in proper condition for allowance, and a Notice of Allowance to that effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: 10/7/2009 By: 

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